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Clozapine as a treatment for catatonia: A systematic review

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ABSTRACT

Catatonia is a neuropsychiatric disorder characterised by altered movement, speech, and behaviour. Clozapine is an established therapy for treatment-resistant schizophrenia, but its role in catatonia has not been systematically examined. In this systematic review, we aimed to assess the evidence for clozapine as a treatment for catatonia.

Full text original research articles in English where at least one patient with catatonia was treated with clozapine were included, provided catatonia did not occur solely in the context of neuroleptic malignant syndrome. Results were tabulated with calculations of summary statistics presented. Risk of bias was assessed with the Tool for Evaluating the Methodological Quality of Case Reports and Case Series.

182 patients were included, 81 from cohort studies and 101 from case reports or case series. 119/182 patients (65 %) had a specified underlying diagnosis of schizophrenia. Over 80 % of reported patients with catatonia had at least partial remission following treatment with clozapine across both cohort studies and case reports and case series. Among the case reports and series, 24/101 patients (23.8 %) followed clozapine withdrawal. Overall, 25 studies were of low quality, 60 of moderate quality and 8 of high quality.

Our findings should be interpreted with caution, as the reliance on case reports, case series and small cohort studies is susceptible to reporting biases, regression to the mean and confounding by other treatments. Future research could use large healthcare databases to ascertain outcomes in those on clozapine with a history of catatonia given the difficulty and expense of conducting randomised controlled trials.

1. Introduction

Catatonia is a neuropsychiatric disorder characterised by altered movement, speech, and behaviour. Although rare in the general population, mean prevalence is approximately 9 % within acute psychiatric populations (Solmi et al., 2018). Although historically associated with schizophrenia, it is now accepted that catatonia may have both psychiatric and organic aetiologies. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) and the International Classification of Disease (ICD-11) both characterise catatonia based on the presence of specific psychomotor symptoms including stupor, catalepsy, mutism, negativism, and waxy flexibility (American Psychiatric Association, 2013; ICD-11, 2022).

Benzodiazepines are usually the first-line treatment for catatonia, irrespective of underlying aetiology, alongside addressing underlying causes and complications (Sienaert et al., 2014). Electroconvulsive therapy (ECT) may also be used to treat underlying depression, in emergencies, or in cases of benzodiazepine-resistant catatonia (NICE, 2003). The long-term use of benzodiazepines may lead to adverse effects on cognition and may generate dependence, whilst electroconvulsive therapy to treat catatonia entails the risks associated with general anaesthesia and reported autobiographical memory loss (Fraser et al.,

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2008). The adverse effects seen in both treatments, alongside uncertain chances of improvement and contraindications for their long-term usage highlight a need to consider other approaches.

Among other drugs, such as NMDA negative allosteric modulators (amantadine and memantine) and sodium channel blockers which selectively block high-frequency discharges (carbamazepine, valproate and topiramate), atypical antipsychotics have been suggested and used off-label to manage treatment-resistant catatonia (Beach et al., 2017; Pelzer et al., 2018; Tanguturi et al., 2019). This is despite concerns that other, typical antipsychotics have historically been reported to precipitate catatonia (Gelenberg and Mandel, 1977) and catatonia has been recognised as a strong risk factor for neuroleptic malignant syndrome (Funayama et al., 2018), so their use is suggested with caution. (Beach et al., 2017; Pelzer et al., 2018).

Clozapine is an atypical antipsychotic with a unique pharmacological profile, binding to serotonergic, α-adrenergic, cholinergic and histaminergic receptors in addition to its relatively low dopamine D_2 receptor occupancy and a higher affinity for the D_4 receptor (Nucifora et al., 2017). It is currently licensed for use in treatment-resistant psychosis (NICE, 2014). Clozapine to treat catatonia may allow for the simultaneous treatment of catatonia and any underlying psychotic disorder in some cases. Since antipsychotic-induced catalepsy in rodents appears to be mediated via antagonism of D_2 receptors (Sanberg, 1980; Kirschbaum et al., 2009), if we accept that this is analogous to antipsychotic-induced catatonia in humans, in theory the relatively weak D_2 antagonism of clozapine compared to other antipsychotics could be advantageous in treating catatonia. Moreover, since neuroleptic malignant syndrome is reportedly rare in clozapine use (Karagianis et al., 1999), clozapine may be a safer option than other antipsychotics.

At a mechanistic level, when considering a putative role of defective GABAergic signalling in catatonia, it has also been suggested that clozapine may treat catatonia similarly to the way in which benzodiazepines are proposed to by stabilise fluctuant $GABA_{A+B}$ activity (Nair et al., 2020; Hirjak et al., 2021). This is further supported by the well-documented phenomenon of catatonia following clozapine withdrawal (Lander et al., 2018).

A 2018 systematic review of catatonia treatment including 31 studies found lorazepam and ECT to be the most investigated treatment options across 9 countries. Clozapine usage was reported to be limited to catatonia with an underlying psychotic disorder, and in such circumstances the use of additional medications in patients often limited discernible conclusions (Pelzer et al., 2018). However, only one study focussing on clozapine usage was included in this review. Another systematic review focussed on drug-withdrawal catatonia, finding that 20 out of 55 reported cases involved clozapine discontinuation, 9 of which responded to re-initiating clozapine treatment. (Lander et al., 2018) This review did not cover the full range of catatonia aetiologies, which may or may not be clozapine-responsive, but its findings raise the interesting prospect that clozapine may be useful in a wider variety of catatonia cases.

In this study, we set out to establish whether there is any evidence to suggest that clozapine is an effective treatment for catatonia by conducting a systematic review of the literature. We note at the outset that this is an area without any randomised controlled trials and that much of the literature consists of case reports and small case series. However, in the absence of higher quality evidence, a synthesis of lower forms of evidence can be clinically helpful and has historically served to advance medical knowledge (Murad et al., 2018).

2. Material and methods

2.1. Search strategy and selection criteria

This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) guidelines (Page et al., 2021) and the PRISMA Checklist is presented in Supplementary Table 1. The study review protocol was not able to be pre-registered on the PROSPERO database because data extraction had already been initiated at an earlier date. The search strategy, selection criteria, study selection technique and data extraction techniques to be used had, however, been prospectively recorded prior to data analysis. A time-stamped protocol for this review with this information is available (Saini, 2021).

We used the NICE Healthcare Databases Advanced Search to search Medline, EMBASE, PubMed, APA PsycINFO and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from inception until 22/06/2021. The overall search strategy was to combine search terms relating to catatonia and those relating to clozapine usage. This was conducted using a comprehensive list of synonyms (including brand names) and subject headings, which were searched for among titles, abstracts and keywords. The full search strategy is presented in Supplementary Table 2.

De-duplication was conducted by one reviewer (NB) and confirmed by a second (JR), for the initial search. Another pair of reviewers (AS and DAG) de-duplicated following the second search. Following pilot screening of ten papers at a full-text level, two sets of two reviewers (NB, JPR for the first search and DAG, LF for the second) screened titles, abstracts, and full texts of extracted articles sequentially. Disagreements on the inclusion at the title or abstract stage led to retention of the article for the next round of screening. Disagreement on the inclusion of a full text led to arbitration with a third reviewer (AS across both searches). The reasons for exclusion of full texts were recorded.

We included English-language original studies published in a peer-reviewed journal where the full text was available. Randomised controlled trials, cohort studies, case-control studies, cross-sectional studies, case series and case reports were all to be included as appropriate study designs. Studies must have had at least one patient with catatonia (as identified by the study author(s)) who was then treated with clozapine. Papers were excluded where catatonia was implied by clinical signs but not identified by a clinician, and where catatonia only occurred in the context of neuroleptic malignant syndrome. Case reports and case series were grouped separately to all randomised controlled trials, cohort studies, case-control studies and cross-sectional studies.

2.2. Data extraction

Extracted data included the citation; study design; number of patients; age; gender; ethnicity; criteria for catatonia diagnosis; Bush-Francis Catatonia Rating Scale (BFCRS) score recorded closest to the time of hospital admission; underlying disorder(s); response to clozapine treatment (‘complete remission’ (i.e. catatonia resolved), ‘partial remission’ (catatonia reduced but did not resolve); or ‘no change’); time from the point of clozapine initiation to outcome; maximum dose of clozapine taken during patient hospitalisation, with corresponding clozapine plasma levels; whether catatonia was documented as temporally related to clozapine withdrawal at any point throughout the patient's admission (defined as catatonia occurring within 14 days after clozapine withdrawal). Data for each paper were independently extracted by two of the authors (NB, LF, DAG, JR). Where reviewers disagreed on the extracted data, a third author (AS, JM) arbitrated.

2.3. Data analysis

Meta-analytic effect sizes could not be calculated, as most studies were case reports or case series. Results were tabulated with calculations of summary statistics presented. Where relevant data were missing, available case analysis was used. As there was no meta-analysis, issues with reporting biases and the degree of certainty of the data are considered in the Discussion.

2.4. Quality assessment

We used the 'Tool for evaluating the methodological quality of case reports and case series' to assess the quality of the included papers (Murad et al., 2018). This tool has 8 questions, scored as 0 or 1, relating to patient selection, ascertainment of outcome and exposure, causality and the level of detail in reporting pertinent information. When assessing whether necessary detail had been included, we deemed age, sex, psychiatric diagnosis and clozapine dose and duration of clozapine use as essential information. This tool was also used for rating of the 6 cohort studies for the purposes of consistency between different types of study.

The total score out of eight was used to ascertain the overall quality of each paper, with scores 0–2 considered low quality, 3–5 moderate quality and 6–8 high quality. This process was carried out by two independent reviewers (LF, DAG). Where there was a disagreement regarding the overall rating of a paper (low/moderate/high), a third reviewer (AS) arbitrated.

3. Results

3.1. Study selection

Initial searches identified 849 studies, of which 93 were eligible, consisting of 79 case reports, 8 case series, and 6 cohort studies (Fig. 1). Studies were published between 1977 and 2021. Within each study, only patients meeting the entire inclusion criteria were included, so it is possible that there would be patients in an included study that were not eligible. 182 patients were included, 101 from case reports or series and 81 from cohort studies.

We found multiple examples of patients treated with clozapine for an underlying disorder such as schizophrenia with historical episodes of catatonia, which were excluded due to a lack of catatonia in the period of interest. Conversely, we found many examples of catatonia which was not treated with clozapine (Chang et al., 2009; Bairrada et al., 2012; Coffey, 2012). As per our criteria, catatonia which existed only in the context of NMS was also excluded (Zalsman et al., 2004; Kasantikul and Kanchanatawan, 2006). Studies in which maintenance clozapine was used only for secondary prophylaxis of catatonia, without primary treatment were also excluded (Samuel et al., 2009; Lin et al., 2016).

3.2. Cohort studies

Data from the 6 cohort studies with 81 patients are shown in Table 1. Age was not specified for the relevant group in any of the studies. Gender was stated in 2 studies, reporting 25 men and 32 women. The only specified underlying diagnosis was schizophrenia, present in at least 55/81 patients (68 %), and unspecified for the remainder of patients. These findings meant it was difficult to make generalisations to catatonia in the context of disorders other than schizophrenia. Catatonia outcome was reported as complete remission in 8 cases (10 %), partial remission in 60 cases (74 %), no change in 6 cases (7 %) and unspecified in 7 cases (9 %). The incidence, or extent of side effects for patients with catatonia taking clozapine was only reported in two of the six studies. One paper describes 2/2 patients as having no side effects (Gaszner and Makkos, 2004), and another paper mentions that 1/6 patients had their medications discontinued due to unspecified side effects (Battegay et al., 1977). Another paper did discuss side effect profiles across a larger, more generalisable cohort of 480 patients taking clozapine, however the extent to which this data can be applied in the context of patients with catatonia is unclear (Naber et al., 1992). Data on ethnicity, initial BFCRS score, time from clozapine initiation to outcome assessment, highest dose of clozapine during admission and final therapeutic clozapine plasma levels were not provided across any of the cohort studies.

3.3. Case reports and case series

Summary data from the 101 patients across the 87 case reports and

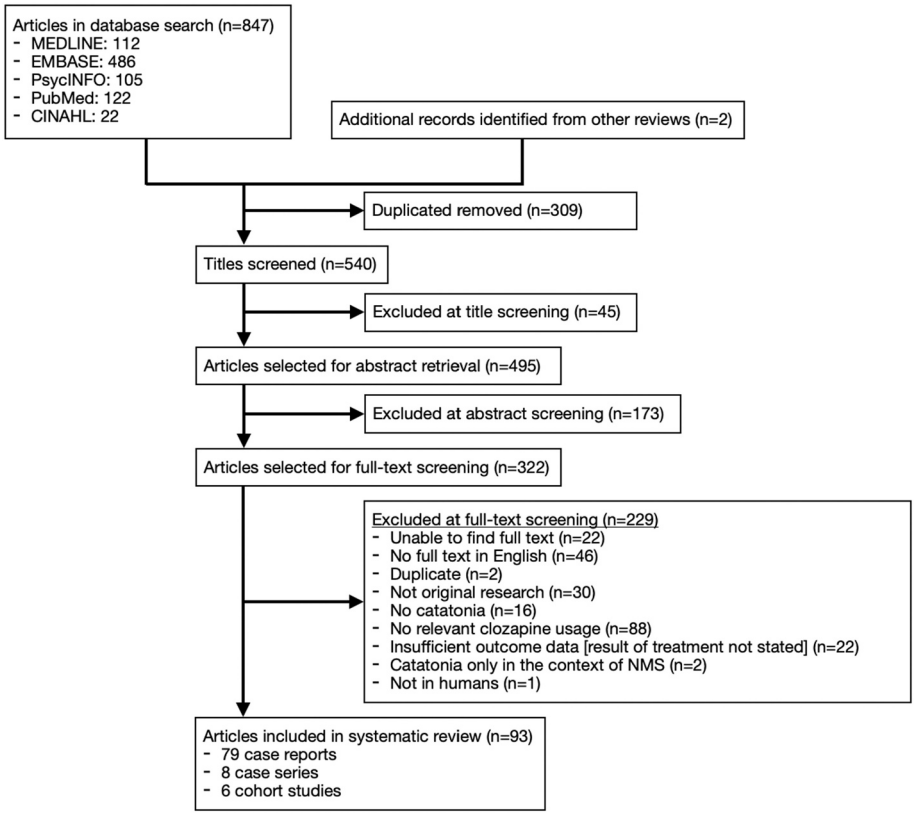

Fig. 1. Flowchart of study selection.
*Extensive efforts to retrieve full texts included searching online via university library pages, Google Scholar and searching for papers on ResearchGate. Access rights from two institutions were used.
NMS = neuroleptic malignant syndrome.

Table 1
Data from cohort studies.

Author, year	N	Gender (M = male, F = female)	Criteria for catatonia diagnosis	Underlying diagnoses	Catatonia documented as due to clozapine withdrawal	Outcome	Time from clozapine initiation to outcome assessment	Other treatments given
(England et al., 2011)	7	–	SCID criteria	–	–	7 Partial remission	Mean 7-week duration	Benzodiazepines and other atypical antipsychotics in all cases
(Battegay et al., 1977)	6	–	–	SZ	–	5 Partial remission 1 No remission	–	2 patients also given other antipsychotics
(Raffin et al., 2015)	5	–	Modified BFCRS	–	–	–	–	1 patient had no other medications, 1 patient had another atypical antipsychotic, 2 patients had benzodiazepines, 1 patient had a typical antipsychotic with a mood stabiliser
(Gaszner and Makkos, 2004)	6	–	–	SZ	–	6 Complete remission	2 cases of continued prophylatic use, others unspecified duration	–
(Bonnot et al., 2008)	2	2M	2 motor signs; or 1 motor sign +1 non-motor sign	SZ	–	–	–	1 patient had benzodiazepines; 1 patient had benzodiazepines, two other antipsychotics and ECT
(Naber et al., 1992)	55	23M 32F	–	SZ	No	2 Complete remission 48 Partial remission 5 No remission	36 cases of continued prophylatic use, others unspecified duration	–

BFCRS = Bush Francis Catatonia Scale, SZ = schizophrenia, ECT = electroconvulsive therapy.

case series are shown in Table 2 with the complete data extraction available in Supplementary Table 3. In brief, patients represented a wide age range (35.1 ± 14.6) and were mostly male (66/101, 65.3 %). A minority specified diagnostic criteria for the diagnosis of catatonia (37/101, 36.6 %). Most had schizophrenia or a related disorder (64/101, 63.4 %). Benzodiazepines (62/101, 61.4 %), other antipsychotics (73/101, 72.3 %) and ECT (41/101, 40.6 %) were commonly used as well as clozapine.

Complete remission occurred in 64/101 (63.4 %), partial remission in 18 (17.8 %) and no change in 19 (18.8 %). Only a minority of catatonia diagnoses were reported to follow clozapine withdrawal (24/101, 23.8 %), among whom following reintroduction of clozapine there was complete remission in 17, partial remission in 4 and no change in 3. Among the 77 patients where catatonia was not documented as related to clozapine withdrawal there was complete remission in 47, partial remission in 14 and no change in 16. Time from clozapine initiation to outcome assessment had a mean of 54.3 (SD 63.6) days in those with complete remission, 72.2 (SD 122.8) days in those with partial remission and 41.3 (SD 68.6) days in those with no change.

3.4. Quality assessment

The results of the quality assessment of the included papers can be found in Supplementary Table 4. Within the cohort studies, 1 was of low quality, 4 of moderate quality and 1 of high quality.

Within the case reports and case series, 24 were of low quality, 56 of moderate quality and 7 of high quality.

4. Discussion

In this systematic review, we examined the literature for all cases where clozapine was used to treat catatonia. We identified 79 case reports, 8 case series, and 6 cohort studies spanning 182 patients across a wide range of ages. Remission rates differed between the study types with 10 % of patients in cohort studies and 63.4 % of those in case reports or series showing full remission, although when full and partial remission are combined, the figures are much more similar (84 % of cohort studies and 81.2 % of case reports or series).

The average time of clozapine use for complete remission of catatonia was 54.3 (SD 63.6) days, compared to 72.2 ± 122.8 days for a partial remission and 41.3 ± 68.6 days for no response. These outcomes are consistent with findings in the wider schizophrenia literature showing that remission generally takes at least several weeks, if not months, on clozapine treatment (Schulte, 2003). Additionally, this short duration of follow up for patients seemingly unresponsive to clozapine treatment raises the prospect that the actual remission rates for clozapine treatment of catatonia may be higher than reported here.

The mean peak dose of clozapine during admission was 322.1 (SD 179.1) mg, a low-normal dose when considering previous works have stated doses between 300 and 750 mg are required for therapeutic efficacy (Schulte, 2003). The 10 patients for which clozapine plasma levels are recorded show an average serum titre of 457.3 ± 156.9 ng/mL, which is within the therapeutic window (Taylor et al., 2021).

This study had several limitations concerning both the underlying studies and their synthesis. In terms of the underlying studies, most patients were described in case reports or case series (55.5 %). There were no controlled treatment trials. By design, these articles cannot demonstrate clozapine is causally associated with improved outcomes in catatonia compared to other medications. Case reports are particularly susceptible to biases such as confirmation bias, hindsight bias and publication bias (Roukis, 2021). In this study, it seems likely that there was a bias towards publishing case reports showing positive outcomes, which was not as reflected in the cohort studies. There is also likely to have been confounding from the other medications co-administered to treat catatonia. In many of these cases, it is possible that catatonia would have resolved spontaneously or that other medications patients were taking also contributed to catatonia resolution. Patients' own experiences of clozapine compared to other psychiatric medications were seldom reported by studies. The BFCRS, whilst clinically helpful in managing catatonia, was also generally a vague description of outcomes/improvement across patients and a breakdown of scores was seldom provided. Finally, the lack of diagnostic classification or formal

Table 2
Summary data from case reports and case studies.

Number of patients, studies	101, 87	
Age, mean ± SD (range) ($N = 101$)	35.1 ± 14.6 (13–74)	
Sex (%)	66 male (65)	
	35 female (35)	
Ethnicity (%)	White	17 (16.8)
	Asian	13 (12.9)
	Black	6 (5.9)
	Other	1 (1.0)
	Mixed	0 (0.0)
	Not specified	64 (63.4)
Diagnostic classification/rating scale for catatonia (%)	BFCRS	22 (21.8)
	BFCRS + DSM-IV	5 (5.0)
	BFCRS + DSM-5	3 (3.0)
	DSM-IV	4 (4.0)
	BFCRS + ICD-10	1 (1.0)
	DSM-5	1 (1.0)
	ICD-10	1 (1.0)
	Not specified	64 (63.4)
Underlying diagnoses (%)	Schizophrenia and related	64 (63.4)
	Schizoaffective	8 (7.9)
	Neurological disorder	4 (4.0)
	Neurodevelopmental	3 (3.0)
	BPAD	3 (3.0)
	Substance misuse	2 (2.0)
	MDD	2 (2.0)
	OCD	1 (1.0)
	Mixed diagnoses	10 (9.9)
	Indeterminate	4 (4.0)
Catatonia documented as related to clozapine withdrawal (%)	Yes	24 (23.8)
	No	77 (76.2)
Initial BFCRS score (mean ± SD) ($N = 26$)	24.0 ± 10.1	
Catatonia outcome (%)	Complete remission	64 (63.4)
	Partial remission	18 (17.8)
	No remission	19 (18.8)
Time from clozapine initiation to outcome assessment, days (mean ± SD)	Complete remission ($N = 49$)	54.3 ± 63.6
	Partial remission ($N = 11$)	72.2 ± 122.8
	No change ($N = 6$)	41.3 ± 68.6
Highest dose of clozapine in treatment, mg ($N = 73$)	315.7 ± 177.2	
Final therapeutic clozapine plasma levels, ng/mL (N = 10)	457.3 ± 156.9	
Other treatments administered for catatonia (%)	Benzodiazepines	62 (61.4)
	Other antipsychotics	73 (72.3)
	ECT	41 (40.6)

BFCRS = Bush-Francis Catatonia Rating Scale, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DSM-V = Diagnostic and Statistical Manual of Mental Disorders, 5th edition, ICD-10 = International Classification of Diseases, 10th edition, BPAD = bipolar affective disorder, MDD = major depressive disorder, OCD = obsessive compulsive disorder, ECT = electroconvulsive therapy.

rating scales for catatonia used represents a limitation to many of the larger, cohort studies as well as the case reports and case series from which data were synthesised.

In terms of the data synthesis, there were also several limitations. Due to the heterogeneity of the cases and their presentation, meta-analysis was not possible. In the quantitative summaries that were presented, there is a risk of a single study disproportionately affecting the results, especially where arbitrary cut-offs had to be used. One particular case of this was in the analysis of remission rates among the cohort studies, where one study accounted for 55 of the total 81 patients. (Naber et al., 1992) This study found a low rate of complete remission of catatonia; with only 3 % patients having an 'almost total reduction in symptoms', a further 59 % patients having a 'marked improvement', 28 % having a slight improvement and 11 % having worsening/no change in symptoms. These findings may be due to the low doses of clozapine used (the average dose across all 480 patients in the study being 190 mg), but it may also be related to how outcomes were categorised. It is unclear how having a 'marked improvement' category may have impacted on the number considered to have 'almost total reduction in symptoms'.

Despite these limitations, these findings do have implications for clinical practice. This paper is the first systematic review to specifically investigate clozapine usage to treat catatonia. Whilst we cannot demonstrate a causal relationship, clozapine use was associated with at least partial remission in 84 % of patients in the cohort studies and 81 % of patients in the case reports or series. Given that clozapine seems to be rarely associated with precipitating or worsening of catatonia and it is an uncommon precipitant of NMS (Karagianis et al., 1999; Mylan, 2018) clozapine could be considered in cases where benzodiazepines and electroconvulsive therapy are not possible or have been unsuccessful. Unlike these other treatment modalities, clozapine is typically used long-term, so it may particularly have a role where catatonia is chronic or frequently relapsing.

There are drawbacks associated with clozapine usage, however. Whilst clozapine is reported to have fewer extrapyramidal symptoms than other atypical antipsychotics (Weiden, 2007), and hypotension due to α1 receptor agonism may be largely avoided by slow uptitration, agranulocytosis, paralytic ileus, myocarditis and cardiomyopathy remain of concern. In addition, abrupt cessation of clozapine can precipitate clozapine-withdrawal catatonia (Lander et al., 2018), which occurred in 23.8 % of all our included case reports or case series. The literature has previously documented withdrawal within 2 weeks of cessation (Lander et al., 2018), but there were multiple articles within our study documenting catatonia as soon as 2 days after cessation (Lee and Robertson, 1997; Rommel et al., 1998). In addition, clozapine taking on average over a month to achieve either partial or full remission means it is slower to take effect than benzodiazepines or ECT treatment which may limit its utility as monotherapy or in acute settings.

The interaction of clozapine and benzodiazepines has historically been of concern, due to incidental case reports and unpublished data from Novartis Pharmaceuticals on around 1700 patients prescribed both drugs concurrently, showing 6 patients (0.31 %) developing respiratory depression/arrest, although 2 cases were attributed to deliberate overdose. However these incidences of cardiorespiratory collapse have been described as 'much lower' compared to European literature (Faisal et al., 1997). Whilst data on side effects were not specifically collected in this study within case reports and case studies, there did not seem to be many cases of clozapine discontinuation due to the interaction of these two drugs. Our data, however, do not seem to document any severe adverse reactions between oral clozapine and diazepam, but only 61 % of patients were documented as receiving benzodiazepines within two weeks of taking clozapine, despite these being considered first-line treatment for catatonia (although it is possible that a large proportion of the remaining patients had already received a benzodiazepine prior to a trial of clozapine). Another study investigating 152 patients prescribed the two drugs concurrently have also found no respiratory, cardiac arrests or sudden deaths (Bitter et al., 2008).

Future research should take the form of well-designed large-scale pharmacoepidemiological studies to assess whether clozapine is associated with better outcomes in catatonia. This could inform an evidence base to justify a clinical trial. Assessing the use of clozapine to treat schizophrenia across a spectrum of catatonic disease states may also help determine indications for clozapine as a treatment for schizophrenia with a prominent motor phenotype.

5. Conclusion

In conclusion, clozapine is an atypical antipsychotic frequently indicated in treatment-resistant schizophrenia, which may be associated with improvement of catatonia in schizophrenia or – more speculatively – catatonia more widely. We document instances of clozapine treating catatonia within the literature and find frequent success reported in this off-label use. We suggest that clozapine use may be considered in the

case of failure or lack of availability of conventional treatments for catatonia such as benzodiazepines or ECT, or earlier where clozapine withdrawal is a likely precipitant. Where clozapine is used for catatonia, treatment response should be closely monitored, and response recorded using a standardised scale such as the BFCRS with consideration to enrolling such participants in research. Clinicians and patients should be prepared to wait at least 8 weeks for a response and for a slow tapering off in the case of non-response given the risk of clozapine-withdrawal catatonia in case of sudden cessation. Data from this study must, however, be interpreted cautiously due to limitations concerning both data derived largely from case-reports and case series and a minority of studies being of high quality. Further research should use large healthcare databases to ascertain outcomes in those on clozapine with a history of catatonia.

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CRediT authorship contribution statement

NB and JPR conceived the project. AS, NB, and JPR planned the project. AS, NB, DAG, LF and JM extracted data. AS, DAG, LF and JM undertook quality assessment. AS conducted the data analysis and wrote the first draft of the report under supervision of JPR. All authors had the opportunity to comment. AS and JPR had final responsibility for the decision to submit for publication.

Declaration of competing interest

The funders had no role in the design, analysis, or decision to publish. MZ has received honoraria for a lecture from Eisai.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.09.021.

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